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| EXAMINER | |
|---|---|
| MITCHELL, LAURA MCGILLEM | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/523,253 | WEISS, SAMUAL | |
| | Examiner | Art Unit | |
| | Laura M. Mitchell | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *01 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1 and 3-40* is/are pending in the application.

4a) Of the above claim(s) *19-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 3-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/1/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

It is noted that claims 1 and 31 have been amended and claim 2 has been cancelled in the amendment filed 10/1/2007. Claims 19-40 have been withdrawn. Claims 1 and 3-18 are under examination.

It is noted that the Office Action mailed 5/18/2007 was inadvertently indicated as a final rejection. Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 3-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because it has been amended to recite the phrase "stem cells derived from neural tissue" and it is not clear how the Applicants intend that the neural stem cells will be derived from neural tissue. Without a clear statement of the process by which the starting material is derivatized, it is not possible to know the metes and bounds of a "derivative" because any given starting material can have many divergent derivatives depending on the process of derivatization. This rejection could be overcome by substituting "isolated" or "obtained" for "derived" in the claim. Claims 3-18 are indefinite insofar as they are dependent on an indefinite claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4 and 10-18 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *in vitro* method of producing oligodendrocytes from multipotent neural stem cells isolated from mouse embryos and also an *in vivo* method to produce oligodendrocytes in mice comprising infusing mice with GM-CSF, does not reasonably provide enablement for a method of producing oligodendrocytes from all types of neural stem cells from any mammal at any developmental stage while the cells are located in a mammal other than a rodent (i.e. humans). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claim 2 has been cancelled and therefore the rejection of claim 2 is mooted. This rejection has been modified.

**This rejection is being maintained for reasons of record in the previous Office Action, mailed 5/18/2007 and for reasons outlined below.**

The Applicant provides herewith a Declaration under 37 C.F.R. § 1.132 by Samuel Weiss ("Weiss Declaration") providing experimental evidence showing that the methods taught herein are enabled. Applicants submit that the data show that GM-CSF promotes the proliferation and survival of oligodendrocytes *in vivo*. Specifically, GM-CSF was infused into 6-week old CD1 male mice for 6 days followed by examination of the factor's effects in the corpus callosum. Applicants submit that the results indicate

that GM-CSF increases production of new oligodendrocytes. Applicants also submit results that indicate that GM-CSF increases the number of terminally differentiated oligodendrocytes in the corpus callosum. The Weiss declaration describes experiments to determine the number of apoptotic terminally differentiated oligodendrocytes in the corpus callosum following ICV infusion of GM-CSF. Dr. Weiss declares that the data indicate that GM-CSF promoted the survival of terminally differentiated oligodendrocytes *in vivo* in the corpus callosum.

Applicants submit that contrary to the Examiner's position that *in vivo* use is not enabled, these data show that GM-CSF enhances the survival of mature oligodendrocytes *in vivo.* Applicants submit that these data demonstrate that one of skill in the art could practice the method commensurate in scope with the claims without undue experimentation.

As noted by the Examiner, the test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation. Further, the MPEP notes at 2164.08 that "[a]ll that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art." Applicants submit that contrary to the Examiner's position that *in vivo* use is not enabled, the data discussed above show that the methods taught and claimed enable one of skill in the art to enhance the survival of mature oligodendrocytes *in vivo.* Applicants submit that one of skill in the art could practice the invention commensurate in scope with the claims without undue experimentation. Applicants also submit that the

existence of references that note the difficulty of developing and performing such methods is completely irrelevant when experimental data, such as that discussed above, is provided to demonstrate that one of skill in the art could perform the disclosed methods.

**The Declaration by Samuel Weiss under 37 CFR 1.132 filed 8/13/2007 is sufficient to partially overcome the rejection of claims 1, 3-4 and 10-18 based upon under 35 U.S.C. 112, first paragraph. Applicant's arguments filed 10/1/2007 have been fully considered but they are only partially persuasive.**

The Weiss declaration provides evidence and support for a method of producing oligodendrocytes *in vivo* in mice using a six-day infusion of GM-CSF into six week old mice. However, the Weiss declaration does not provide sufficient evidence for producing oligodendrocytes comprising contacting multipotent neural stem cells in any other mammal other than a rodent (i.e. human) using any other oligodendrocyte promoting factor. Determination of a sufficient enabling disclosure is determined by a Wands analysis of the Forman factors and the other factors must be considered along with the working example of one aspect of the inventive method.

Applicants submit that the existence of references that note the difficulty of developing and performing such methods is completely irrelevant when experimental data is provided to demonstrate that one of skill in the art could perform the disclosed methods. As discussed below, given the breadth of the claims, state and unpredictability of the art with regard to the mammals in which the method will be practiced, the experimental data provided combined with the specification does not

provide sufficient description so that the skilled artisan could practice the method without excessive trial and error experimentation.

**1) Scope of the claims.** The claims are drawn to an *in vivo* method of differentiation of neural stem cells into oligodendrocytes using an oligodendrocyte promoting factor (OPF), which encompasses a very broad genus of any kind of mammal including humans with demyelinating disease. The claims encompass an embodiment in which the OPF would be administered to the mammal to differentiate the cells. The claims also encompass an embodiment comprising transplanting the stem cells into the mammal and administering an OPF in an effective amount.

**2) State of the Art.** The review authored by Chandran and Compston (of record) was discussed in the previous Office Action (page 3). Chandran and Compston review the potential for neural stem cells in treatment of demyelination repair. Specifically, Chandran and Compston teach that there are interspecies differences in oligodendrocyte potential of neural precursors which cautions the extent to which data from rodents can reliably made to the human system (see page 180, right column, in particular).

**3) Unpredictability of the art.** The unpredictability of a method to produce oligodendrocytes from neural stem cells in a mammal by administering an OPF is manifested in part in the ability of the OPF to specifically affect the neural stem cells without negatively impacting surrounding cells including induction of aberrant growth.

The teaching of Imitola et al (of record) was discussed in the previous Office Action (page 4). Specifically Imitola et al teach that the continuous local infusion of

exogenous cytokines may have positive effects, but that it is not clear how long such manipulation is required in the clinical setting to induce an effect. Imitola et al also teach that a continuous infusion of exogenous cytokines factors may induce hyperplasia and raises questions about the tumorigenic potential of such manipulations. Imitola et al further teach that some trophic factors have pleiotrophic effects on the brain, which may work at cross purposes with each other. The instant specification contemplates practicing the claimed method in demyelinating disorders with areas of demyelination in plaque-like structures. However, Imitola et al teach that addressing multiple lesions that extend throughout the central nervous system is a daunting prospect even with extensively migratory stem cells. Imitola et al caution that careful strategic planning and extensive animal testing will be required before clinical studies can be entertained. Imitola et al summarize that more research is needed to understand the signaling pathways for obtaining highly specific molecular targets without inducing aberrant neurogenesis or tumorigenic proliferation.

**4) Amount of guidance provided.** Besides the experimental information and guidance provided in the Weiss declaration, the specification provides only general guidance that the cells can be administered systemically or *in situ* such as in a lateral ventricle of the brain via any suitable route, depending on the nature of the OPF. The specification and Declaration do not provide specific guidance regarding dosages of any OPF to be administered to multipotent neural stem cells located in any mammal other than a mouse, including human mammals. The specification does not provide any guidance regarding how often the OPF would need to be administered to the neural

stem cells in mammal in order to produce oligodendrocytes. The limitation of mammal encompasses mammals of any age and in any state of health. There is no guidance regarding whether there is any alteration in the method if the mammal is healthy, has been acutely injured or has had a demyelinating disease for many years. The specification does not provide sufficient guidance so that the skilled artisan would know how to use the claimed method to produce oligodendrocytes from multipotent neural stem cells without using excessive and undue trial and error experimentation.

**5) Working examples.** The specification provides examples of a method of producing oligodendrocytes *in vitro*. As discussed above, the Weiss declaration provides an example of the method practiced in a mouse comprising the step of infusing GM-CSF. The specification does not provide any example of a method of producing oligodendrocytes in a mammal besides a mouse from multipotent neural stem cells by contacting them with an effective amount of an OPF when the stem cells are located in a mammal or specifically in the subventricular zone of a mammal.

**6) Nature of the invention.** The invention is drawn to a method to differentiate mammalian multipotent stem cells *in vitro* or *in vivo*, which encompasses stem cell therapy and is a complex and unpredictable aspect of science and medicine.

**7) Level of skill in the art.** The skill in the art is high, but given the state of the art, the unpredictability of the art, the lack of specific guidance and working examples, and scope and nature of the invention, the skilled artisan would have to practice excessive trial and error experimentation in order to be able to use the claimed method. Given the above analysis of the factors which the Courts have determined are critical in

ascertaining whether a claimed invention is enabled, it must be considered that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention to its full scope.

***Claim Rejections - 35 USC § 102***

Applicant's arguments, see REMARKS (pages 9-10), filed 10/1/2007, with respect to claims 1-2, 6-9, 12, 14-15 and 17-18 have been fully considered and are persuasive. Claim 1 has been amended to remove the species G-CSF. Mehler et al teach G-CSF in the production of oligodendrocytes. Mehler do not disclose a method contacting multipotent neural stem cells with an effective amount of granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin 3 (IL-3) or interleukin 5 (IL-5) under conditions that result in production of oligodendrocytes from the multipotent neural stem cells. Claim 2 has been canceled. The rejection of claims 1, 6-9, 12, 14-15 and 17-18 under 35 U.S.C. 102(b) as being anticipated by Mehler et al has been withdrawn.

Applicant's arguments, see REMARKS (pages 10-11), filed 10/1/2007, with respect to claims 1-2, 5, 12-15 and 17-18 have been fully considered and are persuasive. Claim 1 has been amended to remove the species G-CSF and add the limitation that stem cells will be derived from neural tissue. Tennekoon et al teach a method comprising the step of adding G-CSF for the production of oligodendrocytes to mesenchymal stem cells obtained from bone marrow. Tennekoon et al do not disclose a

method contacting multipotent neural stem cells with an effective amount of granulocyte- macrophage colony stimulating factor (GM-CSF), interleukin 3 (IL-3) or interleukin 5 (IL-5) under conditions that result in production of oligodendrocytes from the multipotent neural stem cells. Claim 2 has been canceled. The rejection of claims 1, 5, 12-15 and 17-18 under 35 U.S.C. 102(e) as being anticipated by Tennekoon et al has been withdrawn.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Applicant's arguments see REMARKS (pages 11), filed 10/1/2007, with respect to claim 16 have been fully considered and are persuasive. Claim 1 has been amended to remove the species G-CSF and add the limitation that stem cells will be derived from neural tissue. Tennekoon's mesenchymal stromal cells are not neural stem cells derived from neural tissue. Magil does not appear to make up for this deficiency in Tennekoon. The rejection of claim 16 under 35 U.S.C. 103(a) as being unpatentable over Tennekoon et al (of record) in view of Magil et al has been withdrawn.

***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura M. Mitchell whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem Mitchell, PhD
Examiner
10/10/2007

CELINE QIAN, PH.D.
PRIMARY EXAMINER